PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/11, A61K 39/395, 31/16, C07K 16/28, C12N 5/20, G01N 33/574, 33/577, A61K 31/475, 31/337, A61P 35/00 // C12N 5/06, 5/08, (A61K 39/395, 31:16) (A61K 39/395, 31:475) (A61K 39/395, 31:337)

A3

(11) International Publication Number: WO 00/20576

(43) International Publication Date: 13 April 2000 (13.04.00)

(21) International Application Number: PCT/US99/23162

(22) International Filing Date: 1 October 1999 (01.10.99)

(30) Priority Data:

60/102,816	2 October 1998 (02.10.98)	US
60/124,119	12 March 1999 (12.03.99)	US

(71) Applicant *(for all designated States except US)*: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPT. OF HEALTH AND HUMAN SERVICES, THE NATIONAL INSTITUTES OF HEALTH [US/US]; Office of Technology Transfer, Suite #325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MIELE, Lucio [IT/US]; 2N771 Morningside Avenue, West Chicago, IL 60185 (US). SHIELDS, Leslie, S. [CA/US]; 8507 Capricorn Way #80, San Diego, CA 92126 (US). FUCHS, Chana [US/US]; 4450 S. Park Avenue #1106, Chevy Chase, MD 20815 (US).

(74) Agent: NOONAN, William, D., M., D.; Klarquist, Sparkman, Campbell, Leigh & Whinston, LLP, One World Trade Center, Suite 1600, 121 S.W. Salmon Street, Portland, OR 97204 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report

(88) Date of publication of the international search report:
28 September 2000 (28.09.00)

(54) Title: METHODS AND COMPOSITIONS FOR INDUCING DIFFERENTIATION AND APOTOSIS IN CELLS THAT OVEREXPESS THE NOTCH PROTEIN

(57) Abstract

Methods and compositions are disclosed for inducing differentiation and apoptosis in cells that overexpress Notch proteins. A cell fate determining function of Notch is specifically disrupted at a time when the cell is undergoing differentiation, which causes the cell to undergo apoptosis. The invention includes therapies for tumors that overexpress a Notch protein (such as Notch–1) by inducing differentiation of the cells in the tumor with a differentiation inducing agent, such as HMBA, in combination with an agent that disrupts the function of the Notch protein. At a time during which differentiation has been promoted, and the cell is susceptible to interference with the anti–apoptosis effect of Notch, the function of the Notch protein is disrupted. Disruption of Notch function can be achieved, for example, by a differentiation inducing agent such as HMBA, combined with antibodies that specifically bind to Notch and inactivate it, for example a monoclonal antibody that recognizes Notch–1 EGF–like repeats 11 and 12, such as monoclonal antibodies A6, C11 or F3. Disruption of Notch function can also be achieved by the expression of antisense oligonucleotides that specifically interfere with expression of the Notch protein on the cell, alone or in combination with antineoplastic agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/23162

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 A61K39/395 A61K31/16 C07K16/28 C12N5/20
G01N33/574 G01N33/577 A61K31/475 A61K31/337 A61P35/00
//C12N5/06,C12N5/08,(A61K39/395,31:16),(A61K39/395,31:475),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EMBASE, WPI Data, PAJ, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 07474 A (YALE UNIVERSITY) 14 April 1994 (1994-04-14) claims 32-41,45,61-74,94 ---	1-79
A	D. WAID ET AL.: "Ganglion cells influence the fate of dividing retinal cells in culture." DEVELOPMENT, vol. 125, no. 6, March 1998 (1998-03), pages 1059-1066, XP000907464 Cambridge, GB abstract --- -/--	11-16, 26,33, 48,49, 60,61,77

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/23162

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (A61K39/395,31:337)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	L. SHELLY ET AL.: "Notch-1 inhibits apoptosis in murine erythroleukemia cells and is necessary for differentiation induced by hybrid polar compounds." JOURNAL OF CELLULAR BIOCHEMISTRY, vol. 73, no. 2, 1 May 1999 (1999-05-01), pages 164-175, XP002140810 New York, NY, USA the whole document --- -/--	1-79

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	L. MIELE ET AL.: "Arbiter of differentiation and death: Notch signaling meets apoptosis." JOURNAL OF CELLULAR PHYSIOLOGY, vol. 181, no. 3, December 1999 (1999-12), pages 393-409, XP000907433 Philadelphia, PA, USA page 404, left-hand column, line 32 - line 42	

INTERNATIONAL SEARCH REPORT

...formation on patent family members

International Application No
PCT/US 99/23162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9407474 A	14-04-1994	US 5786158 A	28-07-1998
		AU 685067 B	15-01-1998
		AU 5350394 A	26-04-1994
		CA 2145778 A	14-04-1994
		EP 0662827 A	19-07-1995
		JP 8502170 T	12-03-1996

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-18, 22-24, and 72-74 (all partially, as far as an in vivo method is concerned), and claims 25-51, and 75-79 (all completely) are directed to a method of treatment of the human/animal body, and although claims 52-55 (all partially, as far as an in vivo method is concerned) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
4239-53371		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 23162	01/10/1999	02/10/1998
Applicant		
THE GOVERNMENT OF THE UNITED STATES ..ET AL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

METHODS AND COMPOSITIONS FOR INDUCING DIFFERENTIATION AND APOTOSIS IN CELLS THAT OVEREXPRESS THE NOTCH PROTEIN

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/23162

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

PCT

REC'D 09 FEB 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4239-53371		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/23162	01/10/1999	02/10/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/11		
Applicant		
THE GOVERNMENT OF THE UNITED STATES ..ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/04/2000	07.02.01
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Schwachtgen, J-L Telephone No. +49 89 2399 8933

Form PCT/IPEA/409 (cover sheet) (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged,

(ii) the claim is cancelled,

(iii) the claim is new,

(iv) the claim replaces one or more claims as filed,

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
KLARQUIST, SPARKMAN, CAMPBELL,
LEIGH & WHINSTON, LLP
Attn. Noonan, William D.
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
UNITED STATES OF AMERICA

	Date of mailing *(day/month/year)* 06/07/2000
Applicant's or agent's file reference 4239-53371	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 99/ 23162	International filing date *(day/month/year)* 01/10/1999
Applicant THE GOVERNMENT OF THE UNITED STATES ..ET AL	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

DOCKETED FOR: 10-6-00
9-6-00
COMPUTER ✓
CARD
BOOK
DRAWER ✓
BKPR
ANN. SVE

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nina Vercio

Form PCT/ISA/220 (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/23162

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-59 as originally filed

Claims, No.:

1-79 with telefax of 20/01/2001

Drawings, sheets:

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-3, 5, 11-14, 16-19, 22, 52, 53, 56-58, 67-71,
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-79
Industrial applicability (IA)	Yes:	Claims	19-21, 57-71
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. While the applicant's observations submitted with the amended claims have been considered, the previously expressed negative opinion is nevertheless maintained.

2. Reference is made to the following document

   D1: WO 94 07474 A (YALE UNIVERSITY) 14 April 1994 (1994-04-14)

   D1 discloses therapeutic compositions comprising antisense nucleic acids or anti-Notch neutralizing polyclonal and monoclonal antibodies which antagonize Notch function (page 5, lines 3-9). Said antibodies are directed against the EGF-repeats 11 and 12 of human Notch-1 (page 14, line 7). The Notch anti-sense oligonucleotides comprise a sequence anti sense to the sequence encoding EGF-repeats 11 and 12 of human Notch-1 (page 32, lines 23-27). Said therapeutic compositions are administered to treat and to detect malignacies e.g. cervical cancers by inhibiting Notch function (pages 18-22).

Novelty (Article 33(2) PCT)

3. The antibodies disclosed in D1 anticipate the novelty of product claims 19 and 67-71. Desired functional properties of known products which the skilled person cannot associate with clear technical features, are insufficient to establish novelty.

4. The disclosure in D1 of a method to treat and to detect cervical cancers by inhibiting Notch function, anticipates the novelty of method claims 1-3, 5, 11-14, 16-18, 22, 52, 53 and 56. In a given population of cells, a certain percentage is always undergoing differentiation. This feature is, thus, insufficient to establish novelty.

5. The subject-matter of claims 57 and 58 relates to a method of generating a monoclonal antibody using a plasmid designated pLDL. As the name of a plasmid does not imply any distinguishing technical features, the method cannot be novel.

Inventive step (Article 33(3) PCT)

4. The remaining subject-matter of the present application relates to means and methods to treat tumor cells by administering known antisense oligonucleotides or antibodies which inhibit the function or the expression of Notch-1. The contribution to the closest prior art document D1 consists in the addition to the composition of the compound HMBA which enhances differentiation (description, page 3, lines 19-35).

The technical problem can therefore be formulated as the provision of an effective treatment to induce apoptosis by interfering with the expression or function of Notch-1.

In the present application the technical problem is solved by the provision of a composition comprising a hybrid polar differentiating compound e.g. HMBA in conjunction with an antisense oligonucleotide directed against Notch-1 or an antibody directed against the adhesion-mediating domains EGR-11 and EGR-12 of Notch-1. None of the prior art documents, either alone or in combination, would have led the skilled person to consider this solution without the intervention of inventive skills.

However, the claims of the present application cover subject-matter (e.g. Notch-2, 3, 4; undefined agents capable of "inducing differentiation") for which it has not been shown and for which it is not credible that it solves the technical problem. As a precondition for recognizing inventive step, the technical problem has to be solved in a new and inventive way over the whole scope of the claims. Inventive step, thus, cannot be acknowledged, contrary to the requirements of Article 33(3).

Industrial applicability

Claims1-18, 22-56 and 72-79 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item VIII

Certain observations on the international application

1. Present claims 1-79 refer to a pharmaceutical composition comprising an agent defined as being "differentiation inducing" and a molecule defined by reference to its capacity to "interfere in a cell fate determining function of a Notch protein", the agent and the molecule being present in an "antineoplastic effective" amount and the molecule being administered "at a time during differentiation when Notch is required to prevent apoptosis".

   The use of these functional parameters leads to a lack of clarity within the meaning of Article 6 PCT, as products and methods are defined in terms of a result to be achieved without providing the technical features necessary to achieve the result. As a consequence, it is not possible to compare the parameters the applicant has chosen to employ, with what is set out in the prior art.

2. The application as filed is objectionable for lack of conciseness and clarity (Article 6 PCT), because the claims viewed either individually or taken as a whole make it difficult to construe the claimed subject matter without undue burden. This objection arises because of the number of the claims, their confusing dependencies and unclear functional language.

We claim:

1. A method of inducing apoptosis in a target cell, comprising:

inhibiting a cell fate determining function of a Notch protein in the target cell at a time when the cell is undergoing differentiation; and

inducing differentiation of the cell so that the target cell undergoes apoptosis.

2. The method of claim 1, wherein the target cell is a tumor cell characterized by:

(a) increased expression of the Notch protein; or

(b) increased Notch activity or expression, relative to Notch activity or expression in a same tissue type that is not neoplastic.

3. The method of claim 2, wherein the Notch protein is Notch-1.

4. The method of claim 2, wherein the Notch protein is Notch-2.

5. The method of claim 2, wherein the tumor cell is:

(a) selected from the group consisting of, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy; and

(b) is a tumor cell in a subject.

6. The method of claim 2, wherein the tumor cell is a cervical cancer cell.

7. The method of claim 6, wherein inducing differentiation of the target cell comprises administering an effective amount of a differentiation inducing agent.

8. The method of claim 7, wherein the differentiation inducing agent comprises an agent selected from the group of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachinodate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof.

9. The method of claim 8, wherein the agent is a polar hybrid compound.

10. The method of claim 9, wherein the polar hybrid compound is hexamethylene bisacetamide (HMBA).

11. The method of claim 1, wherein inhibiting the cell fate determining function of Notch protein comprises inhibiting expression of Notch protein in the target cell.

12. The method of claim 11, wherein inhibiting expression of Notch protein comprises exposing the cell to an effective amount of an antisense molecule that specifically blocks expression of Notch protein.

13. The method of claim 12, wherein the antisense molecule includes at least six contiguous nucleotides of a sequence that is complementary to at least a portion of an RNA transcript of a *Notch* gene, and is hybridizable to the RNA transcript.

14. The method of claim 13, wherein the *Notch* gene is *Notch*-1.

15. The method of claim 13, wherein the *Notch* gene is *Notch*-2.

16. The method of claim 13, wherein the antisense molecule comprises at least six contiguous nucleotides from the group consisting of SEQ ID NOS 6, 8, or 11.

17. The method of claim 11, wherein inhibiting the function of Notch protein comprises exposing the cell to a molecule which antagonizes the function of the Notch protein.

18. The method of claim 17, wherein the molecule which antagonizes the function of Notch protein comprises an antibody that specifically binds to Notch, or a portion of the antibody containing a binding domain that specifically binds to Notch.

19. An antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of a differentiation inducing agent.

20. The antibody of claim 19, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

21. A hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

22. The method of claim 18, wherein the antibody is an antibody against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent.

23. The method of claim 22, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

24. The method of claim 18, wherein the Notch protein is Notch-2.

25. A method of inducing apoptosis in a tumor cell that is characterized by increased expression of a Notch protein, comprising:

inducing differentiation of the tumor cell by exposing the tumor cell to a differentiation inducing agent; and

interfering with the Notch function or expression in the tumor cell, at a time during differentiation when the Notch is required to prevent apoptosis, by administering a molecule that specifically interferes with the Notch function or expression.

26. The method of claim 25, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch-1 protein.

27. The method of claim 25, wherein administering the molecule comprises administering an antibody which specifically binds to the Notch-1 protein and interferes with Notch-1 function.

28. The method of claim 25, wherein exposing the tumor cell to a differentiation inducing agent comprises exposing the tumor cell to a differentiation inducing amount of an agent from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D

derivatives, cyclooxygenase inhibitors, arachindonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof that induce differentiation of the tumor cell.

29. The method of claim 25, wherein the tumor cell is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

30. The method of claim 25, wherein the tumor cell is a hematopoietic malignancy or a cervical cancer in which Notch-1 expression is increased.

31. The method of claim 25, wherein:

exposing the tumor cell to a differentiation inducing agent comprises exposing the tumor cell to a differentiation inducing amount of hexamethylene bisacetamide (HMBA); and

the tumor cell is in a subject, to whom the differentiation inducing agent is administered in a therapeutically effective amount.

32. The method of claim 25, wherein administering the molecule comprises:

administering a therapeutically effective amount of an antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent; and

subsequently administering a therapeutically effective amount of a differentiation inducing agent.

33. The method of claim 20, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch-2 protein.

34. The method of claim 32, wherein the monoclonal antibody is selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

35. The method of claim 25, wherein the tumor cell is in a subject, to whom the differentiation inducing agent and monoclonal antibody are administered separately, in a therapeutically effective amount.

36. A method of stimulating differentiation in a target cell, comprising:

administering a therapeutically effective amount of a differentiation agent; and

administering a therapeutically effective amount of an antibody generated against the human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent.

37. The method of claim 36, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b)

C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655; and the target cell is a tumor cell characterized by increased expression of Notch-1 protein.

38. The method of claim 36, wherein the target cell is characterized by increased Notch-1 activity or expression, relative to Notch-1 activity or expression in a same tissue type that is not neoplastic.

39. The method of claim 36, wherein the target cell is a tumor cell in a subject.

40. The method of claim 36, where the target cell is selected from the group consisting of a cervical cancer cell, a breast cancer cell, a colon cancer cell, a melanoma cell, a seminoma cell, a lung cancer cell, and a hematopoietic malignancy cell.

41. The method of claim 36, wherein in the differentiation inducing agent comprises an agent selected from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivative, hormones, hormone antagonisits, and biologic promotors of differentiation, and derivatives thereof.

42. The method of claim 36, wherein in the differentiation inducing agent is a polar hybrid compound.

43. The method of claim 42, wherein the polar hybrid compound is hexamethylene bisacetamide (HMBA).

44. The method of claim 36, wherein stimulating differentiation comprises stimulating terminal differentiation followed by apoptosis.

45. The method of claim 36, wherein stimulating differentiation of the target cell also inhibits a function of Notch-1 which induces apoptosis of the cell.

46. A method of treating a tumor in a subject, wherein the tumor is characterized by an overexpression of Notch protein in cells of the tumor, the method comprising:

administering to the subject an amount of a differentiation inducing agent sufficient to induce at least partial differentiation of cells in the tumor;

administering to the subject a therapeutically effective amount of a molecule that specifically interferes with Notch expression.

47. The method of claim 46, wherein the molecule is selected from the group consisting of an antibody to Notch-1 and an oligonucleotide that specifically interferes with expression of Notch-1 in cells of the tumor.

48. The method of claim 47, wherein the molecule is an antisense oligonucleotide selected from the group of SEQ ID NOS 2, 4 or 7, and the differentiation inducing agent is HMBA.

49. The method of claim 46, wherein the molecule is selected from the group consisting of an antibody to Notch-2 and an oligonucleotide that specifically interferes with expression of Notch-2 in cells of the tumor.

50. The method of claim 46, wherein the molecule is the monoclonal antibody of claim 15, and the differentiation inducing agent is HMBA.

51. The method of claim 46, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655, and the differentiation inducing agent is HMBA.

52. A method of diagnosing and staging tumor cells which overexpress Notch relative to Notch levels in a same tissue type that is not neoplastic, comprising using an antibody generated against human Notch-1 EGF-repeats 11 and 12, that recognizes an extracellular epitope of Notch-1, and that stimulates target cell differentiation in the presence of an effective amount of differentiation inducing agent for immunostaining.

53. The method of claim 52, wherein the tumor cell is selected from the group consisting of: breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

54. The method of claim 53, wherein the antibody is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

55. The method of claim 53, wherein the antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

56. The method of claim 52, wherein the tumor is a cervical cancer or the tumor cells are in a Pap smear.

57. A method of generating an antibody using the plasmid pLD101.

58. The method of claim 57 wherein the antibody is:

a monoclonal antibody; or

a monoclonal antibody that recognizes Notch-1 EGF- repeats 11-12.

59. A pharmaceutical composition comprising a differentiation inducing agent and a molecule that specifically interferes with expression of, or a cell fate determining function of, Notch protein, the agent and molecule being present in a therapeutically effective amount.

60. The pharmaceutical composition of claim 59, wherein:

the molecule comprises an oligonucleotide comprising at least six nucleotides from a sequence complementary to at least a portion of an RNA transcript of a *Notch* gene, and is hybridizable to the RNA transcript; and

the differentiation inducing agent is selected from the group consisting of: retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, and biologic promoters of differentiation, and derivatives thereof that induce differentiation.

61. The pharmaceutical composition of claim 59, wherein the molecule comprises an oligonucelotide selected from the group of SEQ ID NOS 6, 8, or 11.

62. The pharmaceutical composition of claim 60, wherein the molecule is a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

63. A pharmaceutical composition comprising the antibody of claim 19, wherein the antibody is a monoclonal antibody in a therapeutically effective amount sufficient to stimulate target cell differentiation in the presence of a sufficient amount of a differentiation inducing agent.

64. The pharmaceutical composition of claim 63, further comprising:

(a) a therapeutically effective amount of a differentiation inducing agent selected from the group consisting of retinoids, polar compounds, short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachinodate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivative, hormones, hormone antagonists, and biologic promotors of differentiation, and derivatives thereof; and

(b) a pharmaceutically acceptable carrier.

65. The pharmaceutical composition of claim 63, wherein the differentiation inducing agent is HMBA.

66. The pharmaceutical composition of claim 63, wherein the monoclonal antibody is the monoclonal antibody secreted by a hybridoma selected from the group consisting of: a) A6 having A.T.C.C. Accession No. HB12654; b) C11 having A.T.C.C. Accession No. HB12656; and c) F3 having A.T.C.C. Accession No. HB12655.

67. A pharmaceutical composition comprising an antibody selected from the group consisting of: an antibody that specifically binds to Notch, or a portion of the antibody containing a binding domain thereof, or a monoclonal antibody selected from the group consisting of a) a monoclonal antibody secreted by a hybridoma designated A6 having A.T.C.C. Accession No. HB12654; b) a monoclonal antibody secreted by a hybridoma designated C11 having A.T.C.C. Accession No. HB12656; and c) a monoclonal antibody secreted by a hybridoma designated F3 having A.T.C.C. Accession No. HB12655.

68. The antibody of claim 19, wherein the antibody is a monoclonal antibody and the target cell is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

69. A polyclonal antibody generated against biologically active human Notch-1 EGF-repeats 11 and 12 that recognizes an extracellular epitope of Notch-1 and induces differentiation of a tumor cell that overexpresses Notch-1, such that when differentiation of the tumor cells is induced, exposure of the cell to the polyclonal antibody induces apoptosis of the cell.

70. The polyclonal antibody of claim 69, wherein the biologically active human Notch-1 EGP repeats 11 and 12 is not reduced to cleave a disulfide bond.

71. A hybridoma that secretes any of the antibodies of claim 19.

72. The method of claim 1, further comprising treating the target cell with a therapeutically effective amount of another antineoplastic agent at a time that enhances apoptosis in the target cell.

73. The method of claim 72 wherein the other antineoplastic agent comprises vinca alkaloid.

74. The method of claim 73 wherein the vinca alkaloids are selected from the group consisting of vinblastine, Paclitaxel and vincristine.

75. The method of claim 72, wherein the antineoplastic agent is administered substantially concurruently with the agent administered to inhibit a cell fate determining function of a Notch protein in the target cell at a time when the cell is undergoing differentiation, which induces the target cell to undergo apoptosis.

76. A method of inducing apoptosis in a tumor cell that is characterized by increased expression of a Notch protein, comprising:

administering a therapeutically effective amount of a first antineoplasic agent to a subject having a tumor; and

interfering with the Notch function or expression in the cells of the tumor, at a time during differentiation when the Notch is required to prevent apoptosis, by administering a molecule that specifically interferes with the Notch function or expression at a time that enhances an effect of the first antineoplastic agent.

77. The method of claim 76, wherein administering the molecule comprises administering an antisense oligonucleotide that specifically blocks expression of the Notch protein.

78. The method of claim 76, wherein administering the molecule comprises administering an antibody which specifically binds to the Notch protein and interferes with Notch function.

79. The method of claim 76 where in the tumor is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer, and hematopoietic malignancy.

P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Assistant Commissioner for Patents
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n its capacity as elected Office

Date of mailing (day month year) 25 May 2000 (25.05.00)	
International application No. PCT/US99 23162	**Applicant's or agent's file reference** 4239-53371
International filing date (day month year) 01 October 1999 (01.10.99)	**Priority date** (day month year) 02 October 1998 (02.10.98)
Applicant MIELE, Lucio et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 April 2000 (27.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or where Rule 32 applies within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Pascal Prilou